UPLIZNA- inebilizumab injection
Viela Bio, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use UPLIZNA™ safely and effectively. See full prescribing information for UPLIZNA.

UPLIZNA™ (inebilizumab-cdon) injection, for intravenous use
Initial U.S. Approval: TBD

INDICATIONS AND USAGE

UPLIZNA™ (inebilizumab) is indicated for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) to reduce the risk of attacks and associated worsening of disability. (1)

DOSAGE AND ADMINISTRATION

Determine whether there is an active, clinically significant infection before each infusion and do not administer UPLIZNA in the presence of an active infection (2.2)
Pre-medicate with a corticosteroid (methylprednisolone or equivalent), antihistamine (diphenhydramine or equivalent), and an anti-pyretic (acetaminophen or equivalent) before each infusion (2.2)
UPLIZNA is administered as an intravenous infusion. The recommended dose is:

- Initial 300 mg intravenous infusion followed two weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter, starting 6 months from the first infusion (2.1)

Must be diluted before prior to administration (2.3)
Observe the patient for at least one hour after the completion of the infusion (2.3)

DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-use vial (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Infusion reactions: Administer pre-medications to reduce the risk and severity of infusion reactions. Management recommendations for infusion reactions depend on the type and severity of the reaction (5.1)
- Infections: Perform hepatitis B virus (HBV) screening in all patients before initiation of treatment with UPLIZNA. Do not administer UPLIZNA to patients with active hepatitis due to HBV who are positive for HBsAg or HBcAb. For patients who are chronic carriers of HBV [HBsAg+], consult a liver disease expert before starting. UPLIZNA has not been tested when combined with other immunosuppressive therapies. When initiating UPLIZNA in combination with another immunosuppressive therapy or initiating an immunosuppressive therapy while taking UPLIZNA, consider the potential for increased immunosuppressive effects (5.2)
- Vaccinations: Vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion (5.2)

ADVERSE REACTIONS

The most common adverse reactions associated with UPLIZNA treatment were urinary tract infection (11.5%), arthralgia (9.8%), back pain (7.5%), and headache (7.5%) (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Viela Bio, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 7/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

UPLIZNA™ (inebilizumab) is indicated for the treatment of adults with neuromyelitis optica spectrum disorders (NMOSD) to reduce the risk of attacks and associated worsening of disability.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage

UPLIZNA is administered as an intravenous infusion for chronic treatment. The recommended dose is:

- Initial 300 mg intravenous infusion followed 2 weeks later by a second 300 mg intravenous infusion, and a single 300 mg intravenous infusion every 6 months thereafter for chronic usage, starting 6 months from the first infusion

There is no dose adjustment required based on weight or renal or hepatic function.

2.2 Preparation Before Every Infusion

Infection Assessment

Prior to every infusion of UPLIZNA, determine whether there is a clinically significant infection. In case of infection, delay infusion of UPLIZNA until the infection resolves *[see Warnings and Precautions (5.2)]*.

Required Pre-medication

Administer pre-medication with a corticosteroid (e.g. methylprednisolone 80-125 mg IV or equivalent) approximately 30 minutes prior to each UPLIZNA infusion; and an antihistamine (e.g. diphenhydramine 25-50 mg orally or equivalent) and an anti-pyretic (e.g. acetaminophen 500-650 mg orally or equivalent) approximately 30-60 minutes prior to each UPLIZNA infusion. *[see Warnings and Precautions (5.1)]*.

2.3 Preparation and Administration

Preparation

Visually inspect drug product for particulate matter and discoloration. UPLIZNA is a clear to slightly opalescent, colorless to slightly yellow solution, free from or practically free from visible particles. Discard the vial if the solution is cloudy, discolored, or it contains discrete foreign particulate matter.

- Do not shake the vial.
- Obtain an intravenous bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. Do not use other diluents to dilute UPLIZNA as their use has not been tested.
- Withdraw 10 mL of UPLIZNA from each of the 3 vials contained in the carton and transfer a total of 30 mL into the 250 mL intravenous bag. Mix diluted solution by gentle inversion. Do not shake the solution.
- Discard used vials of UPLIZNA.

Storage of Infusion Solution

UPLIZNA does not contain a preservative.

Administer the prepared infusion solution immediately. If not administered immediately, store up to 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) or 4 hours at room temperature prior to the start of the infusion.

Administration

Prior to the start of the intravenous infusion, the prepared infusion solution should be at room temperature.

Administer UPLIZNA under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage potential severe reactions such as serious infusion reactions.

Administer the prepared solution intravenously via an infusion pump at an increasing rate over 90 minutes through an intravenous line containing a sterile, low-protein binding 0.2 or 0.22 micron in-line filter according to the schedule in Table 1.

Table 1. Recommended Infusion Rate for UPLIZNA Administration When Diluted in a 250 mL IV bag

Elapsed Time (minutes)	Infusion Rate (mL/hour)
0-30	42
31-60	125
61-90	333

Observe the patient for at least one hour after the completion of the infusion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 100 mg/10 mL (10 mg/mL) clear to slightly opalescent, colorless to slightly yellow solution in a single-use vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

UPLIZNA can cause infusion reactions, which can include headache, nausea, somnolence, dyspnea, fever, myalgia, rash, or other symptoms. Infusion reactions were observed in 9.2% of NMOSD patients during the first course of UPLIZNA, compared to 10.7% of placebo-treated patients. Infusion reactions were most common with the first infusion, but were observed during subsequent infusions. Most infusion reactions were mild or moderate. Although rare, serious infusion reactions did occur in clinical trials of UPLIZNA.

Reducing the Risk of Infusion Reactions and Managing Infusion Reactions

Administer pre-medication with a corticosteroid (e.g. methylprednisolone 80-125 mg IV or equivalent), an antihistamine (e.g. diphenhydramine 25-50 mg orally or equivalent), and an anti-pyretic (e.g. acetaminophen 500-650 mg orally or equivalent).

Management recommendations for infusion reactions depend on the type and severity of the reaction. For life-threatening infusion reactions, immediately and permanently stop UPLIZNA and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.

5.2 Infections

An infection was reported by a similar proportion of NMOSD patients treated with UPLIZNA (38%) and placebo (41%). The most common infections reported by UPLIZNA-treated NMOSD patients in the randomized and open label periods included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (7.6%), and influenza (6.2%). UPLIZNA was not associated with a higher risk of serious infections. Delay UPLIZNA administration in patients with an active, clinically significant infection until the infection is resolved. UPLIZNA has not been tested together with other immunosuppressants. If combining UPLIZNA with another immunosuppressive therapy, consider the potential for increased immunosuppressive effects.

Hepatitis B Virus (HBV) Reactivation

Risk of HBV reactivation has been observed with other B-cell-depleting antibodies. There have been no cases of HBV reactivation in patients treated with UPLIZNA, but patients with chronic HBV were excluded from clinical trials. Perform HBV screening in all patients before initiation of treatment with UPLIZNA. Do not administer UPLIZNA to patients with active hepatitis due to HBV who are positive for HBsAg or HBcAb. For patients who are chronic carriers of HBV [HBsAg+], consult a liver disease expert before starting and during treatment.

Other Infections

UPLIZNA was not associated with a higher rate of serious infection in NMOSD patients. Although no confirmed cases of progressive multifocal leukoencephalopathy (PML) were identified in UPLIZNA

clinical trials, PML has been observed in patients treated with other B-cell-depleting antibodies. In UPLIZNA clinical trials one subject died following the development of new brain lesions for which a definitive diagnosis could not be established, though the differential diagnosis included atypical NMOSD attack, PML, or acute disseminated encephalomyelitis.

Vaccinations

Administer all immunizations according to immunization guidelines at least 4 weeks prior to initiation of UPLIZNA. The safety of immunization with live or live-attenuated vaccines following UPLIZNA therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until B-cell repletion.

6 ADVERSE REACTIONS

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to UPLIZNA in 225 patients, including 180 patients exposed for at least 6 months and 140 patients exposed for greater than one year.

The safety of UPLIZNA was evaluated in 230 patients in a randomized, placebo-controlled trial in patients with NMOSD, in which 174 patients were exposed to UPLIZNA during randomized, controlled treatment and 213 patients were exposed to UPLIZNA during an open-label treatment period. The population was 18-74 years of age, was 90.9% female, and 213/230 patients were seropositive for autoantibodies to aquaporin-4.

Adverse Reactions in the Pivotal NMOSD Trial

In one randomized, placebo-controlled pivotal trial, 174 NMOSD patients received UPLIZNA 300 mg intravenously on Day 1 and Day 15 of the randomized-controlled period (RCP). Patients continued in the RCP through Day 197. A total of 96.6% of UPLIZNA patients and 94.6% of placebo patients received both the Day 1 and Day 15 doses. Patients in the randomized and open-label (uncontrolled) periods had a total of 357.75 person-years of exposure to UPLIZNA.

The most common adverse reactions during the RCP of the NMOSD clinical trial (incidence ≥ 5% with UPLIZNA and greater incidence than placebo) were urinary tract infection, arthralgia, back pain, and headache (Table 2).

Table 2. Adverse Reactions in Adult Patients with NMOSD with an Incidence of at Least 5% with UPLIZNA and a Greater Incidence than Placebo

	Pivotal NMOSD Trial	
Adverse Reactions	**Placebo N = 56 %**	**UPLIZNA N = 174 %**
Urinary tract infection	8.9	11.5
Arthralgia	3.6	9.8
Back pain	3.6	7.5
Headache	7.1	7.5

Adverse reactions were similar in the RCP and open-label period (OLP). Across both the randomized and open-label treatment in the pivotal trial, the most common adverse reactions (>10%) were urinary tract infection (19.6%), nasopharyngitis (12.9%), infusion reaction (11.6%), and arthralgia (10.2%).

Laboratory Abnormalities in the Pivotal NMOSD Trial

Decreased Immunoglobulins

Consistent with its mechanism of action, average immunoglobulin levels decreased with UPLIZNA use. At the end of the 6.5-month randomized, controlled period, the proportion of patients with levels below the lower limit of normal was as follows: IgA 9.8% UPLIZNA and 3.1% placebo, IgE 11% UPLIZNA and 13% placebo, IgG 3.8% UPLIZNA and 9.4% placebo; IgM 29% UPLIZNA and 16% placebo. The proportion of UPLIZNA-treated patients with IgG levels below the lower limit of normal at year 1 was 7.5% and at year 2 was 14%. The relationship between reduced immunoglobulin levels and infection has not been assessed with UPLIZNA.

Decreased Neutrophil Counts

Neutrophil counts between 1.0-1.5 $x10^9$/L were observed in 6.9% of UPLIZNA-treated patients versus 1.8% of placebo-treated patients. Neutrophil counts between 0.5-1.0 $x10^9$/L were observed in 1.7% of UPLIZNA-treated patients versus 0% of placebo-treated patients. Neutropenia was generally transient and was not associated with serious infections.

Decreased Lymphocyte Counts

A reduction in lymphocyte counts was observed more commonly in patients treated with UPLIZNA than placebo. This finding is consistent with the mechanism of action of B-cell depletion since B cells are a subset of the lymphocyte population.

6.2 Immunogenicity

As with all therapeutic proteins there is potential for immunogenicity. The detection of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay method used and the incidence of immunogenicity is influenced by a number of factors including the assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to UPLIZNA with the incidence of antibodies to other products may be misleading.

In the randomized, controlled period of the pivotal study, 14.3% patients receiving placebo and 9.8% patients treated with UPLIZNA tested positive for ADA at baseline or any post-treatment sample collection. Treatment-emergent antibodies (those that appeared or significantly increased from baseline after administration of UPLIZNA), were detected in 5.6% patients receiving UPLIZNA during the study. The presence of ADA had no apparent impact on the pharmacokinetics, pharmacodynamics, safety, or efficacy of UPLIZNA.

7 DRUG INTERACTIONS

No formal drug-drug interaction studies have been conducted. The primary elimination pathway for therapeutic antibodies is clearance by the reticuloendothelial system. Cytochrome P450 enzymes, efflux pumps, and protein-binding mechanisms are not involved in the clearance of therapeutic antibodies. Therefore, the potential risk of interactions between UPLIZNA and other drugs is low.

Concomitant usage of UPLIZNA with immunosuppressant drugs, including systemic corticosteroids, may increase the risk of infection. Consider the risk of additive immune system effects when co-administering immunosuppressive therapies with UPLIZNA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety of the use of UPLIZNA during pregnancy is unknown. UPLIZNA is a humanized IgG1

monoclonal antibody and immunoglobulins are known to cross the placental barrier. Transient peripheral B-cell depletion and lymphocytopenia have been reported in infants born to mothers exposed to other B-cell depleting antibodies during pregnancy.

One pregnancy occurred in an UPLIZNA-treated patient during the pivotal NMOSD study. The patient discontinued treatment and there were no complications during the pregnancy or delivery, and there were no birth defects in the baby.

Data

Animal Data

UPLIZNA was evaluated in a fertility and embryo-fetal development study in female and male huCD19 transgenic mice at intravenous doses of 3 and 30 mg/kg. The only adverse findings in the study were a treatment-related reduction in fertility index and the number of mice that were pregnant per the number of mice in cohabitation. Importantly, there was no UPLIZNA impact on embryo-fetal development. Treatment with UPLIZNA resulted in the expected pharmacological depletion of total B lymphocytes in peripheral blood of adult mice. In fetal livers, the site of B-cell development in mice, there was a dramatic decrease in B cells in the progeny of dosed mice compared with the progeny of mice that were not dosed. Overall, the results indicate that UPLIZNA is able to cross the placenta and deplete fetal B cells.

A study on the effects of UPLIZNA on pre- and post-natal development was conducted in huCD19 TG mice to determine the potential adverse effects of maternal exposure (from implantation to weaning) on pregnancy, parturition, and lactation of the maternal animals as well as on the growth, viability, development and immune function of the F_1 neonates. Reproductive performance of the F_1 generation was also assessed. Results showed no adverse effects on the F_0 dams, F_1 generation growth, survival, and reproductive development and performance, and F_2 fetuses at any dosage level. The NOAEL for F_0 maternal, F_1 systemic and reproductive, and F_2 embryo/fetal developmental toxicity was considered to be the 30 mg/kg/dose, the highest dose level evaluated. On post-natal day 50, F_1 offspring showed pharmacology-mediated B-cell depletion and histopathologic findings of reduced size/cellularity of splenic white pulp and number/cellularity of lymph node follicles at both dose levels. B cell counts returned to untreated control group levels by post-natal day 357. F_1 pups did show a diminished antibody response to keyhole limpet hemocyanin challenge at both UPLIZNA dose levels after B cells had repopulated. Accordingly, the NOAEL for F_1 development and immunotoxicity could not be determined. The potential effect of UPLIZNA on human B-cell development and function after in utero exposure is not known.

8.2 Lactation

Risk Summary

There are no data on the presence of UPLIZNA in human milk, the effect on a breastfed child, or the effect on milk production. Because many drugs including antibodies are present in human milk, lactating women should be advised to not breastfeed during treatment and for at least 6 months after the last dose of UPLIZNA due to the potential for serious adverse reactions in breastfed infants.

Data

Animal Data

There are no data on the presence of UPLIZNA in the milk of lactating mice from the pre- and post-natal development toxicology study.

8.3 Females of Reproductive Potential

Contraception

Women of childbearing potential should use contraception while receiving UPLIZNA and for 6 months after the last infusion of UPLIZNA.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of UPLIZNA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Of the 230 adult patients with NMOSD evaluated in the pivotal clinical trial, 10 patients were 65 years and older.

11 DESCRIPTION

UPLIZNA is an afucosylated IgG1 monoclonal antibody targeting CD19+ B cells produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. The molecular weight is approximately 149 kDa.

UPLIZNA Injection for intravenous use is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution, free from or practically free from visible particles.

UPLIZNA is supplied in three (3) single-use vials per dose, each containing 100 mg of inebilizumab in 10 mL. Each mL contains inebilizumab (10 mg), L-histidine (1.4 mg), L-histidine hydrochloride monohydrate (2.3 mg), α,α-trehalose dihydrate (40.1 mg), sodium chloride (4.1 mg), polysorbate 80 (0.1 mg) and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Inebilizumab, the active ingredient in UPLIZNA, is a monoclonal antibody that specifically binds to CD19, a cell surface antigen present on pre-B and mature B cell lymphocytes, including plasmablasts and some plasma cells. Following cell surface binding to B lymphocytes, UPLIZNA supports antibody-dependent cellular cytolysis (ADCC) and antibody-dependent cellular phagocytosis (ADCP). B cells are believed to play a central role in the pathogenesis of NMOSD. The precise mechanism by which UPLIZNA exerts its therapeutic effects in NMOSD is unknown but is presumed to involve B-cell depletion and may include the suppression of antibody secretion, antigen presentation, B cell–T cell interaction, and the production of inflammatory mediators.

12.2 Pharmacodynamics

Pharmacodynamics of UPLIZNA were assessed with an assay for CD20+ B cells, since UPLIZNA can interfere with the CD19+ B cell assay. Treatment with UPLIZNA reduces CD20+ B cell counts in blood by 8 days after infusion. In a clinical study of 174 patients, B-cell counts were reduced below the lower limit of normal by 4 weeks in 100% of patients and remained below the lower limit of normal in 94% of patients for 28 weeks after initiation of treatment.

12.3 Pharmacokinetics

The pharmacokinetics of UPLIZNA in NMOSD patients following IV administration was biphasic with a mean terminal half-life of 18 days. The mean maximum concentration was 108 µg/mL (300 mg, second dose on Day 15), and the cumulative AUC of the 26-week treatment period in which NMOSD patients received two IV administrations 2 week apart was 2980 µg•d/mL.

Distribution:

Based on population pharmacokinetic analysis, the estimated typical central and peripheral volume of distribution of UPLIZNA was 2.95L and 2.57L, respectively.

Metabolism:

UPLIZNA is a humanized IgG1 monoclonal antibody that is degraded by proteolytic enzymes widely distributed in the body.

Elimination:

From population pharmacokinetic analysis, the estimated UPLIZNA systemic clearance of the first-order elimination pathway was 0.19 L/day. At low PK levels, UPLIZNA was subject to the receptor (CD19)-mediated clearance, which decreased with time presumably due to the depletion of B cells by UPLIZNA treatment.

Specific Populations

Pediatric Use

UPLIZNA has not been studied in adolescents or children.

Geriatric Use

Based on population pharmacokinetic analysis, age did not affect UPLIZNA clearance.

Gender, Race

A population pharmacokinetic analysis indicated that there was no significant effect of gender and race on UPLIZNA clearance.

Renal Impairment

No formal clinical studies have been conducted to investigate the effect of renal impairment on UPLIZNA. Based on population pharmacokinetic analysis, UPLIZNA clearance was comparable in NMOSD patients with normal and mild/moderate impaired renal function.

Hepatic impairment

No formal clinical studies have been conducted to investigate the effect of hepatic impairment on UPLIZNA. Based on population pharmacokinetic analysis, UPLIZNA clearance was comparable in NMOSD patients with normal and mild/moderate impaired hepatic function.

Drug Interaction Studies

There is no evidence of CD19 or CD20 expression on hepatocytes and CD19/CD20 depletion does not produce chronic systemic alterations of proinflammatory cytokines. An effect of UPLIZNA on the pharmacokinetics of co-administered medications is not expected.

Based on population analysis, commonly used small molecule drugs by patients with NMOSD had no effect on UPLIZNA PK.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No lifetime studies in animals have been performed to determine carcinogenic or mutagenic potential of UPLIZNA. To assess the carcinogenic risk related to long-term depletion of CD19+ B lymphocytes by UPLIZNA, a weight of evidence approach was used. Data from completed nonclinical and clinical studies conducted with UPLIZNA have not revealed any product-specific concern related to an increased risk of malignancies. Additionally, a thorough review of all relevant data pertaining to depletion of B lymphocytes (i.e., information on class effects, knockout mouse models, and human genetic diseases), did not reveal any significant concerns that chronic treatment with UPLIZNA would increase the lifetime risk of cancer in patients.

Results from a fertility and embryo-fetal development study in human CD19 transgenic (huCD19 Tg) mice at doses of 3 and 30 mg/kg demonstrated a treatment-related reduction in fertility index and a

reduction in the number of mice that were pregnant per number of mice in cohabitation.

13.2 Animal Toxicology and/or Pharmacology

The huCD19 Tg mouse was selected as the relevant animal model for testing the pharmacology and toxicology of UPLIZNA because UPLIZNA specifically recognizes human CD19 and has poor or no cross-reactivity to CD19 expressed on cells from nonhuman primates, rodents, or rabbits.

Completed nonclinical studies with UPLIZNA in the huCD19 Tg mouse model demonstrated that there were no adverse effects after repeated intravenous administration. Treatment with UPLIZNA resulted in the expected pharmacological activity of depletion of huCD19+ B cells in peripheral blood and lymphoid tissues. This depletion was reversible in a dose-dependent manner. B-cell depletion also inhibited the accumulation of serum immunoglobulins. The NOAEL following repeated IV administrations of UPLIZNA is 30 mg/kg/week for up to 6 months.

14 CLINICAL STUDIES

14.1 Neuromyelitis Optica Disorder Spectrum (NMOSD)

The efficacy of UPLIZNA for reducing the risk of NMOSD attacks was demonstrated in a pivotal, randomized, double-blind, placebo-controlled clinical trial in adults with AQP4-IgG seropositive or seronegative NMOSD. Patients were randomized and treated in a 3:1 ratio with IV infusions of UPLIZNA 300 mg on Day 1 and on Day 15, or matching placebo, and then followed for a period of 197 days termed the randomized-controlled period (RCP). All potential attacks were evaluated by a blinded, independent, Adjudication Committee (AC), who determined whether the attack met protocol-defined criteria. Patients who experienced an AC-determined attack in the RCP, or who completed the Day197 visit without an attack, exited the RCP and had the option to enroll into an open-label period (OLP) and initiate or continue treatment with UPLIZNA. The study included patients who had experienced at least one acute NMOSD attack in the prior year, or at least 2 attacks in the prior 2 years, requiring rescue therapy, and had an Expanded Disability Severity Scale (EDSS) score ≤ 7.5 (patients with a score of 8.0 were eligible if the Investigator and Medical Monitor agreed the patient was reasonably able to participate).

The primary efficacy outcome was time (days) from Day 1 to onset of an AC-determined NMOSD attack on or before Day 197. Additional outcome measures included worsening from baseline in EDSS at last visit during the RCP, change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart at last visit during the RCP, cumulative total active MRI lesions (new gadolinium-enhancing or new/enlarging T2 lesions) during the RCP, and the number of NMOSD-related in-patient hospitalizations. A patient was considered to have a worsening in EDSS score if one of the following criteria was met: (1) Worsening of 2 or more points in EDSS score for patients with baseline score of 0; (2) Worsening of 1 or more points in EDSS score for patients with baseline score of 1 to 5; (3) Worsening of 0.5 points or more in EDSS score for patients with baseline score of 5.5 or more. Although no comparator was available during the OLP, the annualized attack rate across both randomized and open-label treatment was determined.

In total, 174 patients were treated with UPLIZNA and 56 patients were treated with placebo in the RCP of the study. These included a total of 213 AQP4-IgG seropositive patients and 17 seronegative patients. Baseline demographics and disease characteristics were balanced across the two treatment groups. The mean age was 43 years and 91% were female. The mean disease duration was 2.5 years. At baseline, median EDSS score was 3.5. Background medications for the prevention of NMOSD attacks were not permitted but rescue therapy was initiated as needed for NMOSD attacks. All patients were pre-medicated prior to investigational product administration to reduce the risk of infusion reactions.

Results are presented in Table 3 and Figure 1. In this study, treatment with UPLIZNA statistically significantly reduced the risk of an AC-determined NMOSD attack as compared to treatment with placebo (hazard ratio: 0.272; $p < 0.0001$). Similar results were obtained in the overall study population

and in the AQP4-IgG seropositive population (hazard ratio: 0.227, p < 0.0001; 77.3% reduction in risk of AC-determined NMOSD attack). There were too few seronegative patients to draw conclusions for this population.

A statistically significant improvement with UPLIZNA compared with placebo was demonstrated for three additional endpoints: worsening from baseline in EDSS, cumulative number of total active MRI lesions, and cumulative number of in-patient hospitalizations (Table 3).

Table 3. Efficacy Results in Pivotal Trial in NMOSD

	Treatment Group	
	Placebo N = 56	**UPLIZNA N = 174**
Time to Adjudication Committee-determined Attack (Primary Efficacy Endpoint)		
Number (%) of patients with attack	22 (39.3%)	21 (12.1%)
Hazard ratio (95% CI)[a]	0.272 (0.150, 0.496)	
p-value[a]	< 0.0001	
Additional Efficacy Endpoints		
Worsening from baseline in EDSS at last visit		
Odds ratio (95% CI)[b]	0.370 (0.185, 0.7389)	
p-value[b]	0.0049	
Change from baseline in low-contrast visual acuity score at last visit		
Least squares mean difference in number of optotypes correctly identified[c]	0.134 (1.096)	
p-value[c]	0.9026	
Cumulative number of active MRI lesions among patients with any lesions		
Rate ratio (95% CI)[d]	0.566 (0.387, 0.828)	
p-value[d]	0.0034	
Cumulative number of NMOSD-related in-patient hospitalizations		
Rate ratio (95% CI)[d]	0.286 (0.111, 0.741)	
p-value[d]	0.0100	

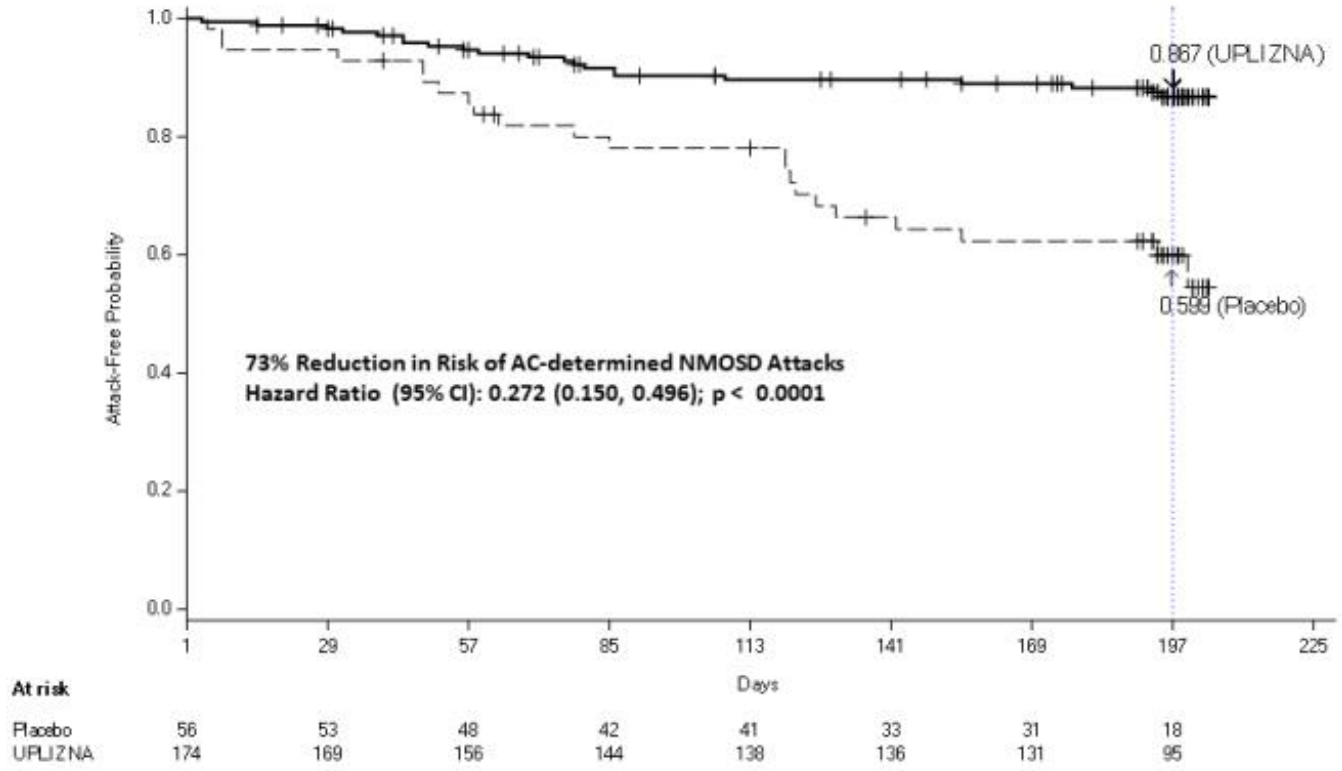
[a] Cox regression method, with Placebo as the reference group.

[b] Logistic regression model.

[c] Analysis of covariance model.

[d] Negative binomial regression.

Figure 1. Kaplan-Meier Plot of Time to First Adjudication Committee-determined NMOSD Attack in the Randomized-Controlled Period (ITT Population)

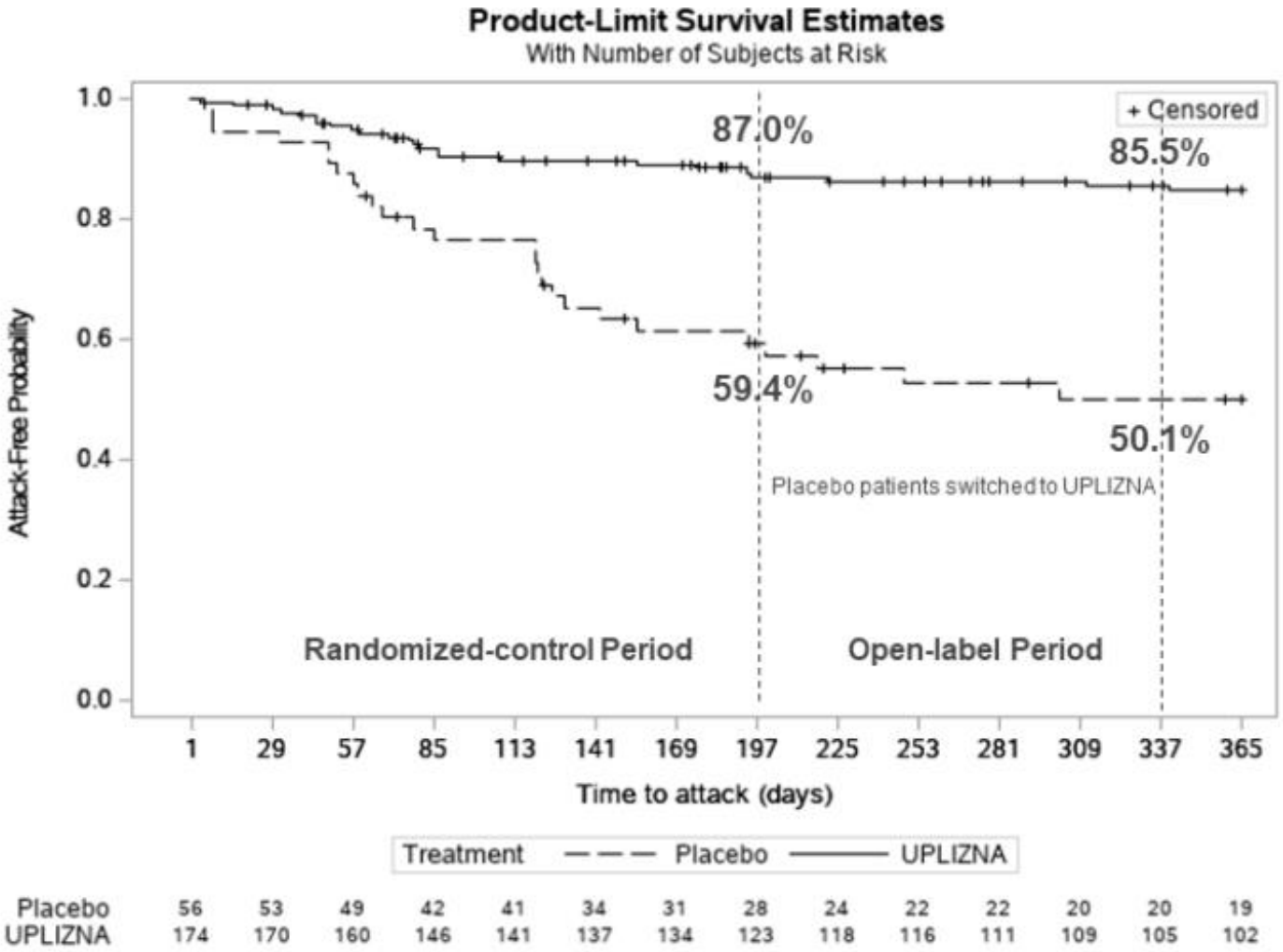


Note: Numbers of patients at risk are shown at each time point.

Across the RCP and OLP, the annualized AC-determined NMOSD attack rate in any patient treated with UPLIZNA was 0.126.

In a post hoc time-to-event analyses for AC-determined NMOSD attack, patient who received UPLIZNA throughout the RCP and OLP showed a persistent treatment effect through 365 days of treatment (Figure 2).

Figure 2. Kaplan-Meier Plot of Time to First Adjudication Committee-determined NMOSD Attack in the Randomized-Controlled Period + Open-label Period (ITT Population)



Note: Patients are classified according to their initial randomization. At the start of the OLP, patients initially randomized to placebo rolled over to UPLIZNA treatment, while patients randomized to UPLIZNA continued with inebilizumab treatment for the OLP. Numbers of patients at risk are shown at each time point.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

UPLIZNA (inebilizumab-cdon) injection is a clear to slightly opalescent, colorless to slightly yellow solution supplied as three (3) single-use vials each containing 100 mg/10 mL of inebilizumab.

- NDC number 72677-551-01: Carton containing three 100 mg/10 mL vials.

16.2 Storage and Handling

- Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light.
- Do not freeze.
- Do not shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide).

Infusion Reactions

Inform patients about the signs and symptoms of infusion reactions and advise them to contact their healthcare provider immediately if they observe signs or symptoms of infusion reactions *[see Warnings*

and Precautions (5.1)].

Infection

Advise patients to contact their healthcare provider for any signs of infection during treatment or after the last dose. Signs include fever, chills, constant cough, or dysuria *[see Warnings and Precautions (5.2)].*

Advise patients that UPLIZNA may cause reactivation of hepatitis B infection and that monitoring will be required if they are at risk *[see Warnings and Precautions (5.2)].*

Advise patients that PML has happened with drugs that are similar to UPLIZNA and may happen with UPLIZNA. Inform the patient that PML is characterized by a progression of deficits and usually leads to death or severe disability over weeks or months. Instruct the patient of the importance of contacting their doctor if they develop any symptoms suggestive of PML. Inform the patient that typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes *[see Warnings and Precautions (5.2)].*

Vaccination

Advise patients to complete any required vaccinations at least 4 weeks prior to initiation of UPLIZNA. Administration of live-attenuated or live vaccines is not recommended during UPLIZNA treatment and until B-cell recovery *[see Warnings and Precautions (5.2)].*

Pregnancy

Instruct patients that if they are pregnant or plan to become pregnant while taking UPLIZNA, they should inform their healthcare provider *[see Pregnancy (8.1)].* Advise females of reproductive potential that they should use effective contraception during treatment and for 6 months after UPLIZNA therapy *[see Females of Reproductive Potential (8.3)].*

Medication Guide

UPLIZNA™ (up-liz'-nah)

(inebilizumab-cdon)

injection, for intravenous use

What is the most important information I should know about UPLIZNA?

UPLIZNA may cause serious side effects, including:

- **Infusion reactions**: UPLIZNA can cause infusion reactions. You will be monitored during your infusion and for at least 1 hour after each infusion of UPLIZNA for signs and symptoms of an infusion reaction. Tell your healthcare provider or nurse if you get any of these symptoms:

  o itchy skin o trouble breathing o nausea o shortness of breath

  o rash o throat irritation or pain o headache o muscle aches

  o hives o feeling faint o swelling of the throat o fast heart beat

  o tiredness o fever o dizziness

  o coughing or wheezing o redness on your face (flushing)

If you develop an infusion reaction, your healthcare provider may need to stop or slow down the rate of your infusion.

- **Infection**: UPLIZNA taken before or after other medicines that weaken the immune system could

increase your risk of getting infections

- **Hepatitis B virus (HBV) reactivation**: Before starting treatment with UPLIZNA, your healthcare provider will do blood tests to check for hepatitis B viral infection. If you have ever had hepatitis B virus infection, the hepatitis B virus may become active again during or after treatment with UPLIZNA. Hepatitis B virus becoming active again (called reactivation) may cause serious liver problems including liver failure or death. Your healthcare provider will monitor you if you are at risk for hepatitis B virus reactivation during treatment and after you stop receiving UPLIZNA.
- **Progressive Multifocal Leukoencephalopathy (PML):** Although no confirmed cases have been seen with UPLIZNA treatment, PML may happen with UPLIZNA. PML is a rare brain infection that usually leads to death or severe disability. Tell your healthcare provider right away if you have any new or worsening neurologic signs or symptoms. These may include problems with thinking, balance, eyesight, weakness on one side of your body, strength, or using your arms or legs.

- **Vaccinations:**
  - Certain vaccines, called "live" or "live attenuated" vaccines, are not recommended in patients receiving UPLIZNA. Please consult your healthcare provider prior to receiving any vaccinations.

What is UPLIZNA?

UPLIZNA is a prescription medicine used to reduce the risk of attacks and associated worsening disability in adults with neuromyelitis optic spectrum disorder (NMOSD). It is not known if UPLIZNA is safe or effective in children.

Who should not receive UPLIZNA?

- Do not receive UPLIZNA if you have an active hepatitis B virus infection.

Before receiving UPLIZNA, tell you healthcare provider about all of your medical conditions, including if you:

- have or think you have an infection
- have ever taken, take, or plan to take medicines that affect your immune system, or other treatments for NMOSD. These medicines could increase your risk of getting an infection.
- have ever had hepatitis B or are a carrier of the hepatitis B virus.
- have had a recent vaccination or are scheduled to receive any vaccinations. You should receive any required vaccines at least 4 weeks before you start treatment with UPLIZNA.
- are pregnant, think that you might be pregnant, or plan to become pregnant. It is not known if UPLIZNA will harm your unborn baby. You should use birth control (contraception) during treatment with UPLIZNA and for 6 months after your last infusion of UPLIZNA.
- are breastfeeding or plan to breastfeed. It is not known if UPLIZNA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take UPLIZNA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive UPLIZNA?

- UPLIZNA is given through a needle placed in a vein (intravenous infusion) in your arm.
- Before treatment with UPLIZNA, your healthcare provider will give you a corticosteroid medicine, an antihistamine, and a fever prevention medicine to reduce infusion reactions (to make them less frequent and less severe). See **"What is the most important information I should know about UPLIZNA?"**
- Your first course of UPLIZNA will be given as 2 separate infusions, 2 weeks apart.
- Your next doses of UPLIZNA will be given as one infusion every 6 months.

- Each infusion will last about 1 hour and 30 minutes, and you will be observed for about 1 additional hour after the infusion.

What are the possible side effects of UPLIZNA?

- **UPLIZNA may cause serious side effects.** See "**What is the most important information I should know about UPLIZNA?"**

The most common side effects include urinary tract infection, joint pain, back pain, and headache. See "**What is the most important information I should know about UPLIZNA?"**

These are not all the possible side effects of UPLIZNA.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of UPLIZNA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use UPLIZNA for a condition for which it was not prescribed. You can ask your pharmacist or healthcare provider for information about UPLIZNA that is written for health professionals.

What are the ingredients in UPLIZNA?

Active ingredient: inebilizumab.

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, α,α-trehalose dihydrate, sodium chloride, polysorbate 80.

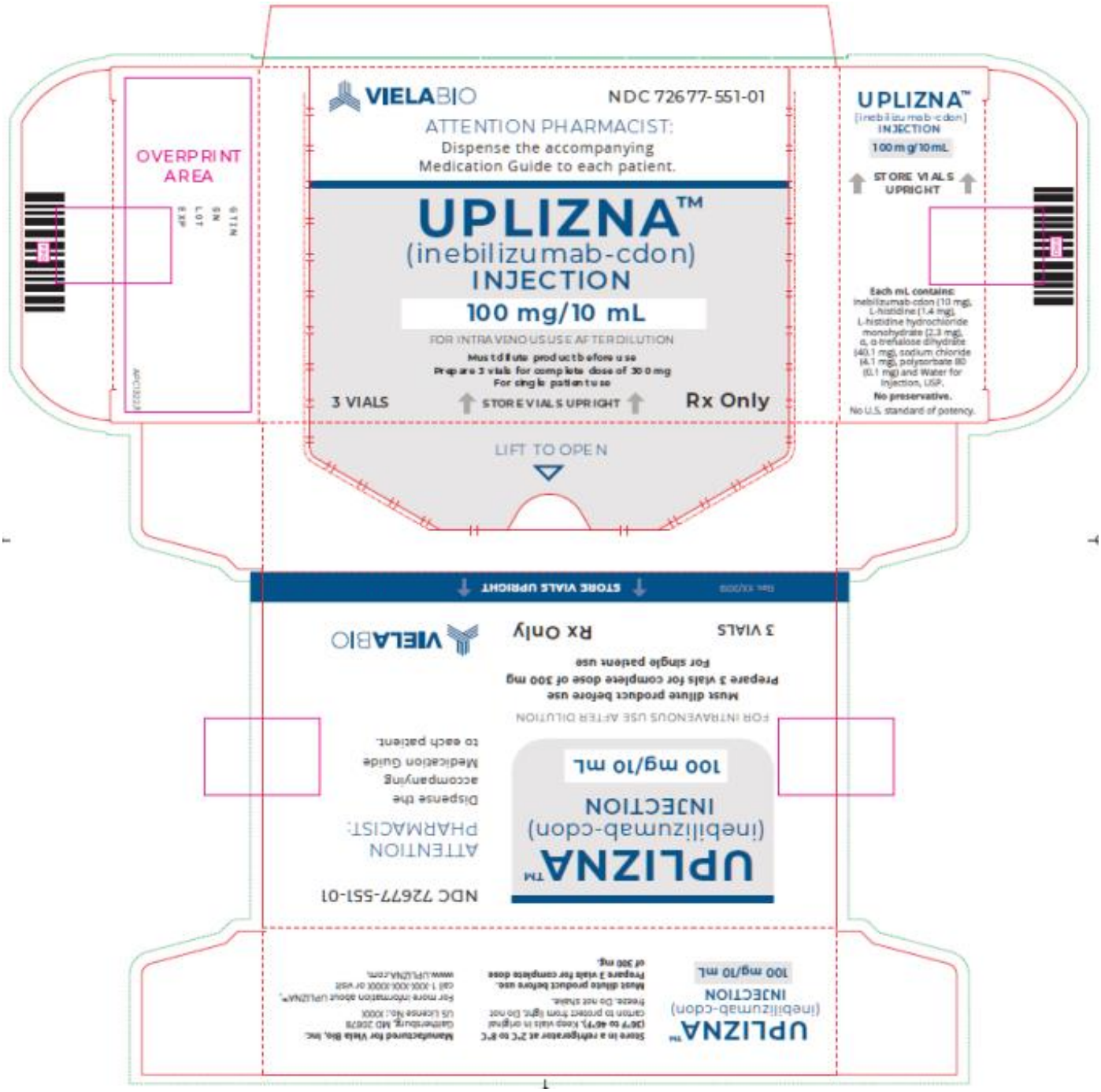
Manufactured for: Viela Bio, Inc., 1 Medimmune Way, Gaithersburg, MD 20878 USA

U.S. License No. xxxxxxx

For more information, go to www.XXXXXX.com or call 1-XXXXXXXXXX.

PRINCIPAL DISPLAY PANEL

NDC 72677-551-01
UPLIZNA
(inebilizumab-cdon)
INJECTION
100 mg/10 mL
Rx Only



UPLIZNA

inebilizumab injection

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:72677-551
Route of Administration	INTRAVENOUS		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
INEBILIZUMAB (UNII: 74T7185BMM) (INEBILIZUMAB - UNII:74T7185BMM)	INEBILIZUMAB	10 mg in 1 mL

Inactive Ingredients	
Ingredient Name	**Strength**
HISTIDINE (UNII: 4QD397987E)	1.4 mg in 1 mL
HISTIDINE MONOHYDROCHLORIDE MONOHYDRATE (UNII: X573657P6P)	2.3 mg in 1 mL
TREHALOSE DIHYDRATE (UNII: 7YIN7J07X4)	40.1 mg in 1 mL
SODIUM CHLORIDE (UNII: 451W47IQ8X)	4.1 mg in 1 mL
POLYSORBATE 80 (UNII: 6OZP39ZG8H)	0.1 mg in 1 mL
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:72677-551-01	3 in 1 CARTON	03/02/2020	
1		10 mL in 1 VIAL, SINGLE-USE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA761142	03/02/2020	

Labeler - Viela Bio, Inc. (081148530)

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